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TITLE: Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis

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14. ABSTRACT Purpose: The most accurate and reliable study design to determine whether the occurrence of TBI increases risk for the development of Alzheimer's disease and related disorders (ADRD) is to identify incident TBI events by medical record review within a defined population and classify each by injury severity, identify matched referents within that same population, and follow both cohorts over time to observe incidence rates of ADRD. Scope: Compared to other study designs, our approach significantly reduces the methodological problems of referral and recall bias, and selective survival, which have limited the scientific community's ability to determine whether TBI is indeed associated with an increased risk of ADRD. There are no published reports of a population-based analysis matching TBI cases, identified by medical record review and classified by injury severity into 3 strata, to population-based referents with non-head trauma. This is particularly important as non-head trauma may also increase the risk of ADRD. Major Findings: 5,430 records of individuals (78% of total) that include 7,565 code dates have been reviewed, yielding 1,428 confirmed cases (yield rate of 26%). 1274 cases (89%) have been matched to their population-based controls.					
15. SUBJECT TERMS Population; epidemiology; dementia; neurocognitive disorders; brain injuries; Parkinsonian disorders					
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1. INTRODUCTION:

Subject: Epidemiological studies linking traumatic brain injury (TBI) and Alzheimer's disease and related dementias (ADRD: including Parkinson's disease, Lewy Body dementia, Frontotemporal dementia, and amyotrophic lateral sclerosis) have yielded conflicting results. These discrepant findings reflect methodological variation in defining TBI, classifying injury severity, and studying clinical cohorts not representative of the broader population. The epidemiology of TBI in military and civilian populations is dominated by the least severe injuries, exposing the greatest number of individuals to potential risk for developing ADRD, yet most previous analysis studying the connection between TBI and ADRD do not include this category of injury severity. **Purpose:** The most accurate and reliable study design to determine whether the occurrence of TBI increases risk for the development of ADRD is to identify incident TBI events by medical record review within a defined population and classify each by injury severity, identify matched referents within that same population, and follow both cohorts over time to observe incidence rates of ADRD. **Scope:** Mayo Clinic has been at the forefront of population-based epidemiological research related to both TBI and ADRD, and has a unique capability to study their association. Compared to other study designs, our approach significantly reduces the methodological problems of referral and recall bias, and selective survival, which have limited the scientific community's ability to determine whether TBI – including number and severity – is indeed associated with an increased risk of ADRD. To our knowledge, there are no published reports of a population-based analysis matching TBI cases, identified by medical record review and classified by injury severity into 3 strata (definite or 'moderate-severe'; probable or 'mild'; possible or 'concussive'), to population-based referents with non-head trauma. This is particularly important as non-head trauma may also increase the risk of ADRD.

2. **KEYWORDS:** Population; epidemiology; dementia; neurocognitive disorders; brain injuries; Parkinsonian disorders

3. ACCOMPLISHMENTS:

Major Goals

- a. Mayo Clinic/Olmsted Medical Center IRB Approval
- b. HRPO approval
- c. Identify all potential individuals with TBI. Target completion 1-6 months

- d. Confirm and classify TBI events. Target completion 3-24 months
- e. Match individuals with a confirmed TBI to age- and sex-matched individuals from the population without a TBI. Target completion 6-24-months
- f. Determine presence of ADRD based on medical record review and assess relationship between TBI and ADRD. Target completion 24-36 months
- g. Data sharing via FITBIR. Target completion 12-36 months:

What was accomplished under these goals?

- a. Mayo Clinic/Olmsted Medical Center IRB Approval
 - 1) major activities: achieved 25-Aug-2015/16-Nov-2015
- b. HRPO approval
 - 1) major activities: achieved 03-Dec-2015; HRPO continuing review submitted 22-Sep-2016
- c. Identify all potential individuals with TBI. Target completion 1-6 months
 - 1) major activities: computer-based screening of Rochester Epidemiology Project data sets for potential cases.
 - 2) specific objectives: Construct a list of potential individuals consisting of all Olmsted County residents with any diagnosis suggestive of head injury or TBI from 1/1/1985 through 12/31/2012
 - 3) significant results: 6,939 individuals with 9,665 code dates for index injuries that occurred at or after the age of 40 years have been identified within the study period.
- d. Confirm and classify TBI events. Target completion 3-24 months
 - 1) major activities: All available clinical data is reviewed either in the paper or Electronic Medical Record including, but not limited to, general history notes, ED notes, hospital records, radiological imaging findings, surgical records, and autopsy reports.
 - 2) specific objectives: Confirm incident TBI events
 - 3) significant results: 5,430 records of individuals (78% of total) that include 7,565 code dates have been reviewed, yielding 1,428 confirmed cases (yield rate of 26%).

- e. Match individuals with a confirmed TBI to age- and sex-matched individuals from the population without a TBI. Target completion 6-24-months: 1274 cases (89%) have been matched to their population-based controls.
- f. Determine presence of ADRD based on medical record review and assess relationship between TBI and ADRD. Target completion 24-36 months: Nothing to Report
- g. Data sharing via FITBIR. Target completion 12-36 months:
 - 1) major activities:
 - 2) specific objectives: Enter the Mayo TBI Classification System into the FITBIR data dictionary as unique data elements; A de-identified data set of the subjects used in this research will be sent to the FITBIR Informatics System when the data is made ready for analysis and this analysis is complete. FITBIR variables will include: The Abbreviated Injury Scale (AIS) as it relates to assigning non-head trauma severity to TBI cases and their controls; Age; Birth Country name; Death cause; Education type and year count; Ethnicity USA category; Gender type; Imaging study and date; Injury cause; Injury date and time; Injury ICD e-codes; Loss of consciousness (LOC) duration; LOC indicators; post-traumatic amnesia (PTA) duration range; Race category; Seizure indicators; TBI mechanism type; and Vital status.
 - 3) significant results: All 1,428 cases have been assigned pseudo-GUIDs and quarterly uploads to FITBIR continue.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

- a. Completion of the task of matching individuals with a confirmed TBI to two (2) age- and sex-matched individuals from the population without a TBI.
- b. For TBI events that were associated with other non-head injuries, each of the accompanying non-head injuries will be assigned an empiric measure of severity, to which the Trauma Mortality Prediction Model will be applied to assign an overall measure of non-head injury severity to each individual.
- c. For all individuals, determine the whether they have a diagnosis of any ADRD after the index date and up to December 31, 2014, and type of ADRD.
- d. Enter the Mayo TBI Classification System into the FITBIR data dictionary as unique data elements per protocol and with FITBIR consultation. This process continues.
- e. All cases have been assigned pseudo-GUIDs. A de-identified data set of the subjects used in this research will be sent to the FITBIR Informatics System when the data is made ready for analysis and this analysis is complete. FITBIR variables will include: The Abbreviated Injury Scale (AIS) as it relates to assigning non-head trauma severity to TBI cases and their controls; Age; Birth Country name; Death cause; Education type and year count; Ethnicity USA category; Gender type; Imaging study and date; Injury cause; Injury date and time; Injury ICD e-codes; Loss of consciousness (LOC) duration; LOC indicators; post-traumatic amnesia (PTA) duration range; Race category; Seizure indicators; TBI mechanism type; and Vital status.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

During funding years 1 and 2, Dr. Brown's work and expertise has been focussed on completing Major Tasks 1, 2, and 3. Dr. Brown has spent sufficient time and effort to direct the team to this point. Accomplishing the final Major Task (Major Task 4: Determine the presence of Alzheimer's disease and related dementias – ADRD – in the confirmed cases and controls based on medical record review and assess their relationship between TBI and ADRD) will be focussed on completing the pre- and post-incident injury TBI burden of cases by nurse abstractors, neuroepidemiology related to ADRD, and statistical analysis. We intend to reduce Dr. Brown's dedicated research time on this analysis to 1% from 5% for the duration of the funding period to allow for this focussed effort. We have achieved our project milestones as outlined in the application and remain on schedule for project completion by the end of the funding period. This change in dedicated effort will not affect this schedule for achieving our project goals and aims, while allowing for sufficient time for Dr. Brown's involvement in dissemination activities. This reduction in investigator time was formally requested to Amber Stillrich, Grants Specialist, US Army Medical Research Acquisition Activity 17Sept2017.

6. PRODUCTS:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>Allen Brown, MD</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0001-7228-3351</i>
Nearest person month worked:	<i>0.5</i>
Contribution to Project:	<i>Dr. Brown is responsible for all administrative aspects of the grant and research activity, including IRB approval, working with Dr. Mielke to oversee the epidemiological design of the study and the data abstractors. Dr. Brown provides clinical direction about case definition, injury classification, and assigning severity level for non-head trauma of cases and controls.</i>

Name:	<i>Michelle Mielke, PhD</i>
Project Role:	<i>Co-investigator</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>0.5</i>
Contribution to Project:	<i>Dr. Mielke oversees the epidemiological design of the study and the data abstractors.</i>
Name:	<i>Jane Emerson</i>
Project Role:	<i>Nurse Abstractor</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>9</i>
Contribution to Project:	<i>Medical record abstraction.</i>
Name:	<i>Dawn Pereda</i>
Project Role:	<i>Nurse Abstractor</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	<i>9</i>
Contribution to Project:	<i>Medical record abstraction.</i>
Name:	<i>Jeanine Ransom</i>
Project Role:	<i>Data Analyst</i>
Researcher Identifier (e.g.	

ORCID ID):	
Nearest person month worked:	7
Contribution to Project:	Identification of potential cases, data cleaning and review, identifying control subjects, identifying overlap between TBI cases and controls, and their development of Alzheimer's disease and related dementias.

Has there been a change in the active other support of the PD/PI (s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Quad Chart

Understanding the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis

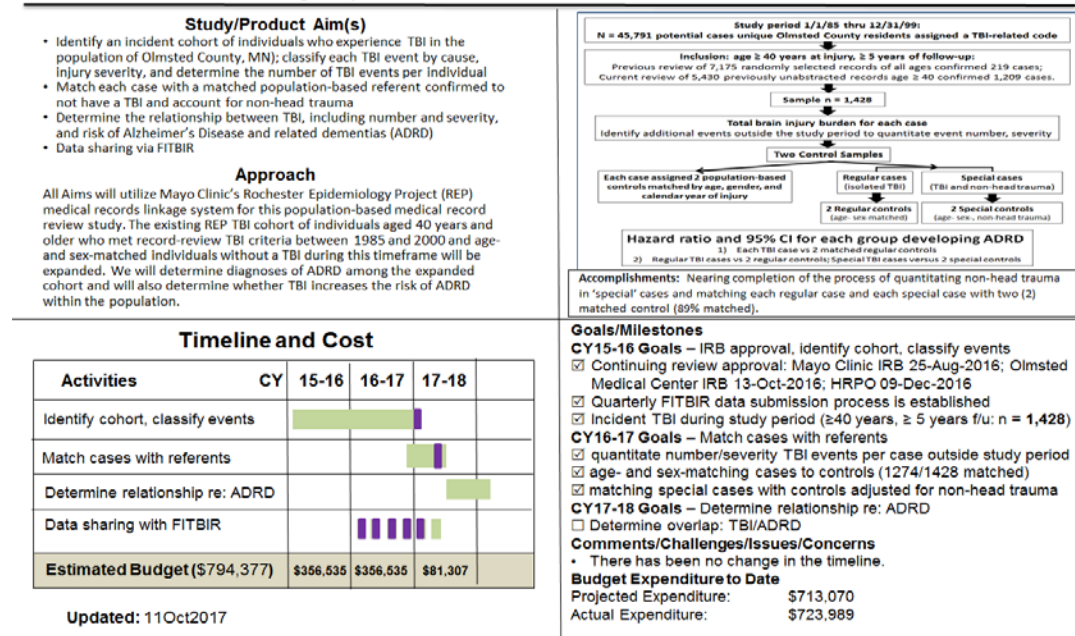
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PI: Allen Brown

Org: Mayo Clinic and Foundation, Rochester

Award Amount: \$794,377



9. **APPENDICES:**

Nothing to Report